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13 # PATENT APPLICATION

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Holder : *Idem* 71
74 **Agent :**

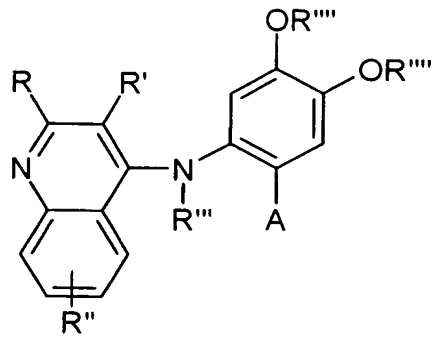
54 **Veratrylaminoquinolines.**

72 Invention of :

33 32 31 Conventional priority :

The present invention relates to new derivatives of 4-aminoquinoline characterised by an N-substituent belonging to the veratrole family.

The compounds concerned by the invention are defined by the following general formula :-



In this formula, R represents a hydrogen atom or an alkyl residue or a phenyl residue or a halogen ;
R' represents a hydrogen atom or an alkyl residue or an aryl residue ;
R'' represents one or several optional substituents which may be one or more halogens and/or one or more alkyl residues and/or one or more alkoxy groups and/or one or more nitro groups ;
R''' represents a hydrogen atom or an alkyl residue ;
R'''' represents a methyl, ethyl or propyl residue ;
A represents an atom of fluorine, chlorine or bromine.

The invention also concerns the addition salts formed between the compounds thus defined and organic or mineral acids.

The compounds of the invention possess antimalarial, amoebicidal, anthelmintic and/or anti-coccidial properties.

The invention concerns the non-pharmaceutical applications, resulting from the said properties.

In these applications, the products of the invention may be used in any form, either alone or two or more together ; they may also be used in the form of liquid, moldable or solid compositions.

A composition may be comprised of one or several products of the invention, mixed with one or several inert products and/or one or more products possessing one or more activities similar to or distinct from those being the subject of the invention.

A liquid composition may be, for example, a solution or a suspension or a dispersion in water or in any suitable liquid.

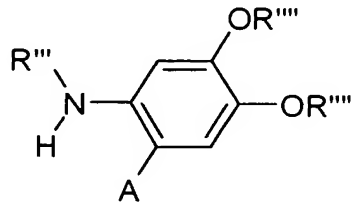
A solid composition may, for example, be presented in the form of powder, granules, tablets, agglomerates or of doses containing one or other of these forms.

A moldable composition may, for example, be a solution or suspension or a dispersion in a moldable body, such as a grease, a paraffin, a wax, an oil or a resinous and/or adhesive substance ; it may constitute, for example, a liniment, an ointment, a cream, a balm, an unguent or patch.

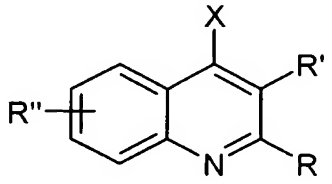
A composition, according to the spirit of the invention, may be, for example, a food or an alimentary premix, containing one or more products of the invention, the whole thing being intended for the alimentation of animals and at the same time the prevention of helmi(n)thiases, coccidioses and other parasitic conditions in these animals.

A composition can also be, according to another example, a powder containing a dispersing agent and one or more of the products of the invention, the whole thing being

intended for making drinks for the animals with the aim of protecting them against infectious diseases.
The invention also concerns the manufacture of the compounds previously defined following a process consisting of the action of a substituted aniline of general formula :



in which A, R''' and R'''' are as has been previously stated, on a 4-haloquinoline of the following general formula :



in which X is a halogen, R, R' and R'' being as has been previously stated for the compounds of the invention.

The reaction is carried out preferably in an inert liquid serving as solvent or support such as, for example, a hydrocarbon, a ketone, an alcohol, a phenol, an N,N-dialkylamide or a dialkyl sulphoxide.

Preferably the operation is carried out at a temperature above ambient temperature in order to speed up the rate of the reaction.

According to a variation the operation is carried out in the presence of an acid acceptor, such as an organic or mineral base, with the aim of removing the halogenated acid formed in the reaction.
Some examples of preparation are given below ; these examples are purely illustrative and do not limit the invention in any way.

Example 1

4-(2-Bromo-4,5-dimethoxyanilino)-7-chloroquinoline

In 500 millilitres of phenol heated to 100°C, are introduced 198 grams (1 mole) of 4,7-dichloroquinoline and 232 grams (1 mole) of 4-amino-5-bromoveratrole ; the mixture is heated slightly until the reaction itself maintains a temperature which is not allowed to exceed 130/140°C in order to avoid the formation of troublesome by-products ; when the reaction has reduced in intensity, it is heated again so as to maintain it at 120°C for 6 hours. It is allowed to cool to 70/80°C and poured into a solution comprising 250 grams of sodium hydroxide in 4 litres of water ; the compound formed is extracted using chloroform ; the solution is dried over sodium sulphate then the chlorofom evaporated under reduced pressure.

Example 2

Replacing the 4,7-dichloroquinoline, in the reaction of example 1, with another 4-haloquinoline, the compounds hereinafter, in particular, are obtained :

4-Chloroquinoline used	Compound obtained
4-chloro-6,7-dimethoxyquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-6,7-dimethoxyquinoline
4-chloro-6,7-diisobutylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-6,7-diisobutylquinoline
4,7-dichloro-2-methylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-7-chloro-2-methylquinoline
4,7-dichloro-2-phenylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-7-chloro-2-phenylquinoline
4-chloro-2-methyl-8-nitroquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-2-methyl-8-nitroquinoline
4,6-dichloroquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-6-chloroquinoline
4,8-dichloroquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-8-chloroquinoline
4,7-dichloro-3-phenylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-7-chloro-3-phenylquinoline
4,7-dichloro-8-methylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-7-chloro-8-methylquinoline
4-Bromo-2-methylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-2-methylquinoline
4-chloro-3-methylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-3-methylquinoline
4-chloro-7-methylquinoline	4-(2-Bromo-4,5-dimethoxyanilino)-7-methylquinoline

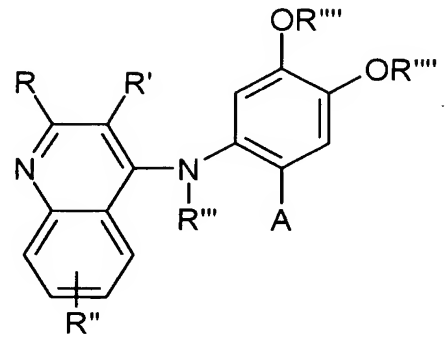
Example 3

Replacing the 5-bromo-4-aminoveratrole, in the reaction of example 1, by another substituted aniline, the compounds hereinafter, in particular, are obtained :

Substituted aniline used	Compound obtained
4-amino-5-chloroveratrole	4-(2-chloro-4,5-dimethoxyanilino)-7-chloroquinoline
4-amino-5-fluoroveratrole	4-(2-fluoro-4,5-dimethoxyanilino)-7-chloroquinoline
2-bromo-4,5-diethoxyaniline	4-(2-bromo-4,5-diethoxyanilino)-7-chloroquinoline
2-chloro-4,5-diethoxyaniline	4-(2-chloro-4,5-diethoxyanilino)-7-chloroquinoline
2-fluoro-4,5-diethoxyaniline	4-(2-fluoro-4,5-diethoxyanilino)-7-chloroquinoline
2-bromo-4,5-dipropoxyaniline	4-(2-bromo-4,5-dipropoxyanilino)-7-chloroquinoline
2-chloro-4,5-dipropoxyaniline	4-(2-chloro-4,5-dipropoxyanilino)-7-chloroquinoline
2-fluoro-4,5-dipropoxyaniline	4-(2-fluoro-4,5-dipropoxyanilino)-7-chloroquinoline

CLAIMS

1. Novel industrial products comprised by the compounds defined by the following general formula :



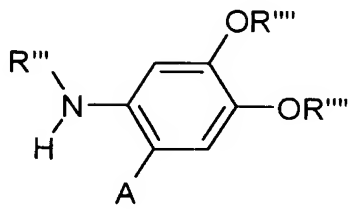
in which R represents an atom of hydrogen or an alkyl residue or a phenyl residue or a halogen ;
R' represents a hydrogen atom or an alkyl residue or an aryl residue ;
R'' represents one or several optional substituents which may be one or more halogens and/or one or more alkyl residues and/or one or more alkoxy groups and/or one or more nitro groups ;
R''' represents a hydrogen atom or an alkyl residue ;
R'''' represents a methyl, ethyl or propyl residue ;
A represents an atom of fluorine, chlorine or bromine.

2. Novel industrial products, in accordance with the first claim, comprised by the following compounds :

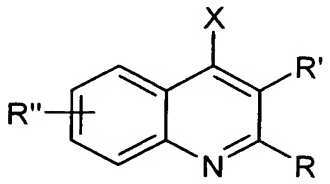
4-(2-bromo-4,5-dimethoxyanilino)-7-chloroquinoline
4-(2-bromo-4,5-dimethoxyanilino)-6,7-dimethoxyquinoline
4-(2-bromo-4,5-dimethoxyanilino)-6,7-diisobutylquinoline
4-(2-bromo-4,5-dimethoxyanilino)-7-chloro-2-methylquinoline
4-(2-bromo-4,5-dimethoxyanilino)-7-chloro-2-phenylquinoline
4-(2-bromo-4,5-dimethoxyanilino)-2-methyl-8-nitroquinoline
4-(2-bromo-4,5-dimethoxyanilino)-6-chloroquinoline
4-(2-bromo-4,5-dimethoxyanilino)-8-chloroquinoline
4-(2-bromo-4,5-dimethoxyanilino)-7-chloro-3-phenylquinoline
4-(2-bromo-4,5-dimethoxyanilino)-7-chloro-8-methylquinoline
4-(2-bromo-4,5-dimethoxyanilino)-2-methylquinoline
4-(2-bromo-4,5-dimethoxyanilino)-3-methylquinoline
4-(2-bromo-4,5-dimethoxyanilino)-7-methylquinoline
4-(2-chloro-4,5-dimethoxyanilino)-7-chloroquinoline
4-(2-fluoro-4,5-dimethoxyanilino)-7-chloroquinoline
4-(2-bromo-4,5-diethoxyanilino)-7-chloroquinoline
4-(2-chloro-4,5-diethoxyanilino)-7-chloroquinoline
4-(2-fluoro-4,5-diethoxyanilino)-7-chloroquinoline
4-(2-bromo-4,5-dipropoxyanilino)-7-chloroquinoline
4-(2-chloro-4,5-dipropoxyanilino)-7-chloroquinoline
4-(2-fluoro-4,5-dipropoxyanilino)-7-chloroquinoline

3. Novel industrial products comprised by the salts formed between the compounds stated in claims 1 and 2 and organic and mineral acids.

4. Manufacturing process consisting in the action of a substituted aniline of general formula :



in which A, R''' and R'''' are as has been stated in the first claim, on a 4-haloquinoline of the following general formula :



in which R, R' and R'' are as is stated in the first claim,
X being a halogen.
5. Liquid, moldable or solid compositions, for non-pharmaceutical use, containing one or several of the products defined in claims 1 to 3.